Diagnostic Testing For Cushing's Syndrome

By James Findling, MD

A screening evaluation for the possibility of Cushing's syndrome should be considered in any patient with signs and symptoms of excessive cortisol secretion. Abnormal weight gain, particularly in the central location accompanied by hypertension, diabetes, or hyperlipidemia should always signal the possibility of Cushing's syndrome. Many patients with this disorder will also have facial rounding with the so-called "moon faces." Accumulation of fat above the clavicles or behind the neck are also common features of excessive cortisol secretion. Some patients will also present with osteoporosis (particularly rib fractures) and some have muscle weakness. The presence of wide purplish striae (stretch marks) in the abdomen or elsewhere can also be a symptom of Cushing's syndrome. The majority of patients with Cushing's syndrome have some type of neuropsychiatric problem (particularly depression) or even some cognitive impairment. Fatigue is almost always present in patients with Cushing's. In addition, women with the polycystic ovary syndrome should also all be screened for the possibility of Cushing's syndrome.

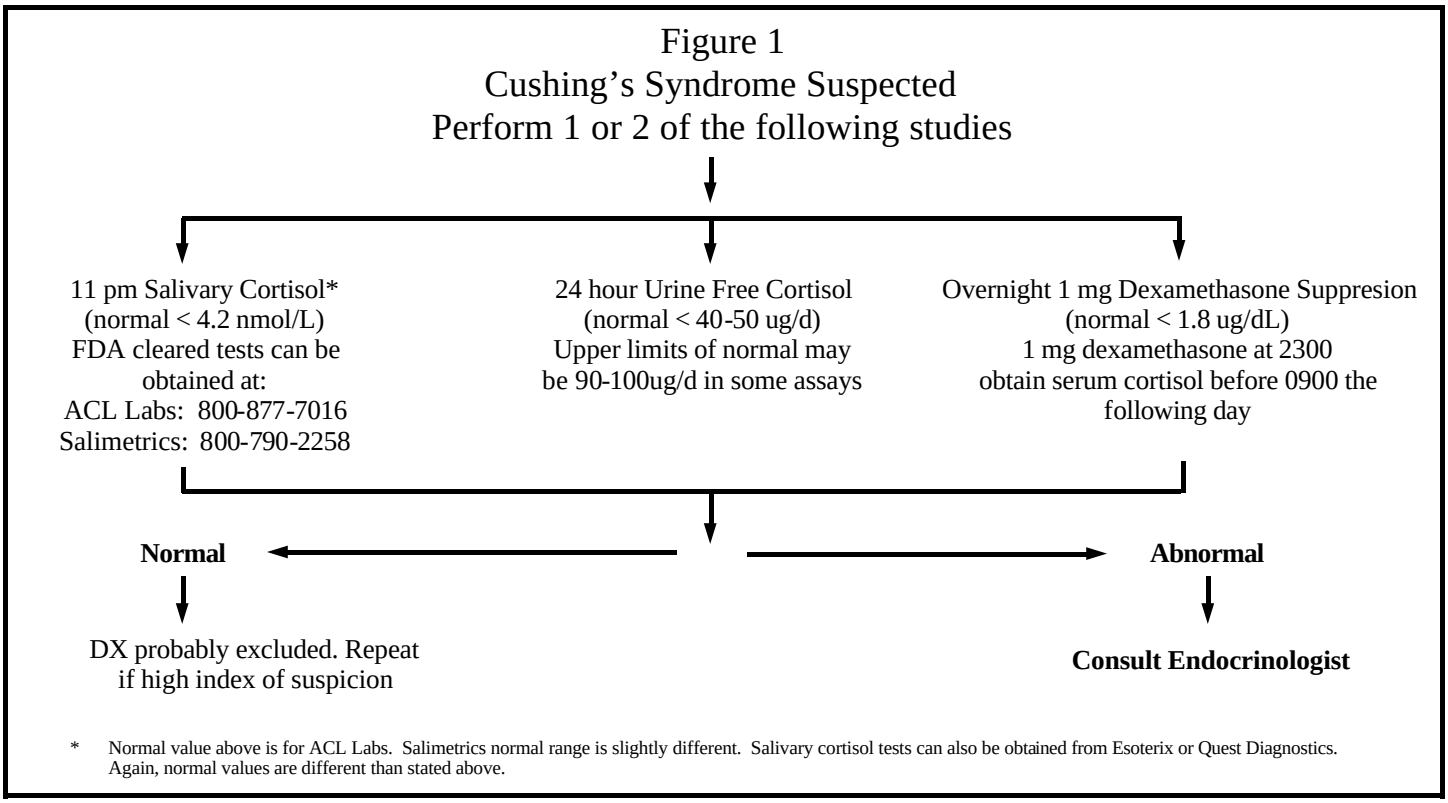
The most appropriate diagnostic approach to patients with suspected Cushing's syndrome is somewhat controversial; however, four diagnostic studies are currently used: late-night salivary cortisol, 24 hour urine free cortisol, low-dose dexamethasone suppression, and the dexamethasone-CRH test. Three tests are summarized in Figure 1.

Late-Night Salivary Cortisol

Late-night salivary cortisol is emerging as the most sensitive diagnostic test for Cushing's syndrome. Elevated cortisol between 11:00 p.m. and midnight appears to be the earliest detectable abnormality in patients with this disorder. Cortisol secretion is usually very low at this time of the day, but in patients with Cushing's syndrome, the value is virtually always elevated. Although this is a relatively new test, it is currently the most widely studied single test for the diagnosis of Cushing's syndrome with at least eight independent studies from all over the world demonstrating sensitivity of 93-100% for the diagnosis of Cushing's syndrome. In the United States, there is only one FDA-approved assay for the measurement of salivary cortisol in the diagnosis of Cushing's syndrome. Collection of saliva requires special sampling tubes; however, this is a very easy test for patients to perform and can be done on multiple occasions. Salivary cortisol is very stable at room temperature and the samples can actually be mailed to a reference laboratory. Normal levels of late-night salivary cortisol virtually exclude the diagnosis of Cushing's syndrome.

Urine Free Cortisol

24 hour urine free cortisol has, until recently, been considered the gold standard for the diagnosis of cortisol excess. A 24 hour urine free cortisol level does reflect the cortisol secretion throughout an entire day. Although the majority of



* Normal value above is for ACL Labs. Salimetrics normal range is slightly different. Salivary cortisol tests can also be obtained from Esoterix or Quest Diagnostics. Again, normal values are different than stated above.

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patients with Cushing's have elevated levels of urine free cortisol, it is becoming increasingly evident that many patients with mild Cushing's syndrome will actually have normal levels of urine free cortisol. In other words, a normal 24 hour urine free cortisol does not exclude the diagnosis of Cushing's syndrome and additional testing is always needed. In addition, there are many conditions which may increase urine free cortisol that are not Cushing's syndrome, specifically depression, chronic alcoholism, and eating disorders.

Low-Dose Dexamethasone Suppression Testing The low-dose dexamethasone suppression testing has been used for four decades as a diagnostic tool in the evaluation of patients with suspected Cushing's syndrome. Dexamethasone is a synthetic steroid that should suppress the cortisol production in normal subjects to a very low level. Currently, the most widely used test is the administration of a small dose of dexamethasone (1 mg) at 11:00 p.m. followed by a measurement of serum cortisol early the following morning. It is now clear that normal subjects should suppress their cortisol level to a very low level (<1.8 µg/dl). This test using this strict criterion will provide approximately 95-97% sensitivity in the diagnosis of Cushing's syndrome; however, some patients with mild Cushing's syndrome will suppress their serum cortisol to levels even lower than this. This test is still widely employed and certainly can be useful in combination with the other tests previously mentioned.

Dexamethasone CRH Test

In patients with equivocal results, combination of dexamethasone suppression in combination with a stimulation test using a hormone called CRH can be useful in making the diagnosis of Cushing's syndrome. CRH is a hypothalamic hormone which normally stimulates ACTH from the pituitary and subsequently cortisol from the adrenal gland. This study should only be performed in a setting where there are endocrinologists who have had experience with the test and ensure it is performed properly.

DIFFERENTIAL DIAGNOSTIC TESTING

Once the diagnosis of Cushing's syndrome has been established, its cause must be identified. The majority of patients with Cushing's syndrome have an ACTH-secreting tumor usually from the pituitary gland (Cushing's disease) or a non-pituitary tumor (ectopic ACTH syndrome). Some patients with Cushing's syndrome may have a tumor in their adrenal glands secreting excessive cortisol or occasionally may have nodules in both adrenal glands that are hypersecreting.

ACTH Levels

The first step in distinguishing the type of Cushing's syndrome is the measurement of ACTH. Patients with ACTH-secreting tumors will either have a normal or elevated level of ACTH. In contrast, patients with adrenal Cushing's will have a subnormal level.

MRI Pituitary

Distinguishing a pituitary from a non-pituitary ACTH-secreting tumor may be a diagnostic challenge. Since the majority of patients with ACTH-secreting tumors have a pituitary lesion (often very small), a MRI of the pituitary gland with gadolinium enhancement is always the initial approach. When an unequivocal pituitary tumor (>5 mm) is identified with MRI, further diagnostic evaluation may not be needed depending on the clinical presentation. In such a case, referral to a skilled pituitary neurosurgeon may be recommended; however, it should be noted that at least 10% of the population have incidental tumors in the pituitary gland demonstrated on MRI. This means that at least 10-15% of patients with the ectopic ACTH syndrome also have an abnormal MRI of the pituitary gland.

Petrosal Sinus Sampling

In patients in whom the diagnosis is not certain based on pituitary imaging, the single best test to confirm the presence or absence of an ACTH-secreting pituitary tumor is a procedure called inferior petrosal sinus sampling. This procedure requires a skilled invasive radiologist who can sample blood from the veins (inferior petrosal sinuses) that drain the pituitary. ACTH as well as other pituitary hormones reach the systemic circulation through veins called the inferior petrosal sinuses. A catheter can be placed in both of these veins at the same time and blood sampled for ACTH before and after the administration of CRH (which stimulates ACTH) and at 2, 5, and 10 minutes. This invasive study should be performed at a center with extensive experience in the procedure and has a diagnostic accuracy of 95-98%.

High-Dose Dexamethasone Suppression Testing

Endocrinologists continue to perform high-dose dexamethasone suppression testing to distinguish a pituitary from a non-pituitary ACTH-secreting tumor. Unfortunately, this test is not helpful in this regard and should be abandoned.

Computed Tomography of the Adrenal Glands

In patients who do not have an ACTH-secreting tumor and thereby low ACTH levels, the problem usually resides within the adrenal gland. CT scanning of the adrenal glands will be helpful in identifying whether this represents a solitary cortisol-producing tumor from the adrenal gland or whether there are large nodules in each adrenal gland resulting in cortisol excess.

Editor's Note: Dr. Findling is an Endocrinologist and is the Director of the Endocrine-Diabetes Center at St. Luke's Medical Center in Milwaukee, Wisconsin. Dr. Findling has been involved with Cushing's for many years. More detailed information on testing is available in a recent review article: ***A physiologic approach to diagnosis of the Cushing syndrome, Raff H, Findling JW. Ann Intern Med. 2003 Jun 17;138(12): 980-91.***